REMARKS

I. Status of the Application and Claims

With entry of this Amendment, new claims 17-98, are pending in the application. Applicants have canceled prior claims 1, 3, 7, 8, 10-12, 14, and 16 without prejudice or disclaimer in favor of the new claims. Appendix 1 is a table relating the prior claims to the new claims, and identifying support for the new claims in the specification. No new matter has been entered by claims 17-98.

Applicants have also amended the title of the application to conform language in the title to language in the claims. As noted in the published specification at [0002], the terms "meticillin" and "methicillin" are synonyms. In the Amendment filed April 30, 2007, Applicants amended the claims to recite "methicillin." For consistency, they have now similarly amended the title. No new matter has been entered into the application by the amendment.

II. The Claims Are Definite

The Office rejects claims 1, 3, 7, 8, and 10-12 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. According to the Office, the phrase "after an enriching phase" is unclear because no guidance is provided by the claim language, or the specification, as to what the sample is enriched for. Office Action, page 2. Applicants traverse.

The rejected claims have been canceled, thus the rejection is moot as to those claims and the Office should withdraw it. Dependent method claims 56 and 82 recite that "the sample is inoculated after an enriching phase." In view of that claim language, Applicants provide the following remarks.

Applicants submit that one of skill in the art would readily understand the meaning of the claim language at issue. As stated in the published specification at paragraph [0013]:

> The media according to the invention make it possible to detect meticillin-resistant bacteria using an inoculum streaked on a dish, whereas the majority of the methods of the prior art use a deposit of approximately 10^4 to 10^5 bacteria on the agar. The media according to the invention can be used directly from a sample from a patient, or after an enriching phase.

One of skill in the art would understand that, in contrast to inoculating the media of the invention directly with a sample from a patient, an "enriching phase" means first culturing the patient sample to enrich for methicillin-resistant bacteria and using the resulting culture to inoculate the claimed media. "Enrichment" in the context of bacterial culture was a concept well known to the skilled artisan at the time of the invention. For example, "Biology of Microorgansims," a textbook of general microbiology published in 1979, discloses that in an enrichment culture method "a medium or set of incubation conditions are used that are selective for the desired organism, and that are inhibitory, or counterselective, for undesired organisms." *See* Exhibit 1, page 604.

Thus, one of skill in the art would understand the claim language "after an enriching phase" as meaning that the sample is enriched for the methicillin-resistant *Staphylococcus aureus* which the claimed method detects. Accordingly, the claim language is definite.

III. The Claims Are Patentable Over the Prior Art

A. Merlino in View of Felten

The Office has maintained the rejection of claims 1, 10, and 11 as allegedly being unpatentable under 35 U.S.C. § 103(a) over Merlino *et al.*, New Chromogenic

Identification and Detection of *Staphylococcus aureus* and Methicillin-Resistant *S. aureus*," J. Clin. Microbiol., 38:2378-80 (June 2000) ("Merlino") in view of Felten *et al.*, "Evaluation of Three Techniques for Detection of Low-Level Methicillin-Resistant *Staphylococcus aureus* (MRSA): a Disk Diffusion Method with Cefoxitin and Moxalactam, the Vitek 2 System, and the MRSA-Screen Latex Agglutination Test," J. Clin. Microbiol., 40:2766-71 (August 2002) ("Felten"). Office Action, page 3. Applicants traverse for the reasons of record supplemented as follows.

Merlino is characterized by the Office as "report[ing] that methicillin-resistant bacteria reliably grew on methicillin/oxacillin-doped plates . . . ." Office Action, page 3. That characterization, however, is inaccurate. In Table 2, Merlino reports that 100% of hospital-acquired MRSA strains showed positive colored growth on CHROMagar medium supplemented with methicillin or oxacillin. However, only 30% of community-acquired MRSA demonstrated positive colored growth on the same antibiotic-supplemented medium. *Id.* Thus, taking the results reported in Merlino as representative, if one tested 100 hospital-acquired MRSA strains and 100 community-acquired MRSA strains one would fail to detect 70 community-acquired MRSA strains among the 200 total strains tested. Merlino discusses this uncertainty in accurately detecting community-acquired MRSA strains at length:

> Multi-drug-resistant MRSA strains were reliably detected on the medium [supplemented with methicillin or oxacillin] (100%) with similar color changes, and all were positive for PBP 2a. **However, non-multi-drug-resistant community acquired MRSA grew inconsistently on the chromogenic medium. Only 4 of 12 (30%) such isolates grew on the supplemented CHROMagar (Table 2).** Different incubation temperatures (30, 35, and 37°C) did not affect this result (data not shown). . . .
>
> **The supplementation with oxacillin or methicillin allows nosocomial [hospital acquired] multi-drug resistant MRSA to be detected, which**

> **was not the case with non-multi-drug-resistant community acquired MRSA.** Non-multi-drug-resistant community acquired MRSA are of increasing clinical significance and represent a growing proportion of community-acquired *S. aureus* infections from outpatient clinics. . . . **The cause of these organisms' growth anomaly on the test chromogenic medium remains unclear but may reflect active cotransportation of methicillin intracellularly with the chromogenic moiety.** In the presence of methicillin or oxacillin, the chromogenically linked substrates may affect the cell membrane potential during permeation, leading to nonspecific membrane disorganization or induced cell death. Research is currently being undertaken to define these phenomena in these community-acquired non-multi-drug-resistant MRSA strains. **Further evaluation of this new chromogenic medium with direct clinical specimens is needed before this medium can be used for routine direct screening for MRSA.**

Merlino, page 2380 (emphasis added).

Clearly, Merlino demonstrates uncertainty regarding whether antibiotic-supplemented CHROMager medium was generally useful for detecting MRSA given the poor results observed with community-acquired MRSA strains. This uncertainty undermines the Office's contention that the combination of Merlino and Felten would have given a person of ordinary skill in the art a reasonable expectation of success. Without that reasonable expectation, *prima facie* obviousness has not been established and the Office should withdraw the rejection.

Felten's teaching combined with Merlino does not provide the requisite expectation of success because Felten teaches that an entirely different technique, the disk diffusion method, is more effective than the method of Merlino, which uses culture medium containing antibiotic incorporated throughout the medium. In making the rejection, the Office selectively focuses on Felten's teaching of cefoxitin and moxalactam while ignoring that Felten uses those antibiotics in a disk diffusion method. As a reference method used for comparison, Felten also tests an Oxascreen agar

assay, which involves Mueller-Hinton agar plates containing 2% NaCl and oxacillin incorporated into the agar at a concentration of 6 ug/ml. Felten, page 2767, 2nd column. The overall sensitivity of the Oxascreen agar assay for detecting MRSA clinical isolates was 94%. *Id.*, page 2768, Table 1. The cefoxitin and moxalactam disk diffusion assays, on the other hand, were both 100% sensitive. *Id.*

In discussing these results, Felten consistently links the perfect sensitivity of these two antibiotics to the disk diffusion assay. Felten never generalizes the results obtained with these antibiotics to other methods. Felten states that "the cefoxitin and moxalactam **disk diffusion methods** were the best-performing tests for routine detection of all classes of MRSA." Felten, page 2766, abstract (emphasis added). At page 2769, in the first paragraph of the discussion, Felten states:

> The cefoxitin and moxalactam **disk diffusion methods** were found 100% sensitive and specific for MRSA under all conditions tested, except for one isolate under test conditions of a low-density inoculum and incubation at 30°C. **This implies that the cephamycin disk test (cefoxitin or moxalactam) is an available alternative to the oxacillin disk method** for routine antibiotic susceptibility testing at 37°C. (Emphasis added.)

Not only did the oxacillin disk method unfavorably compare to the cefoxitin and moxalactam disk methods (*see* Felten, page 2768, Table 1), the Oxascreen agar assay compared unfavorably to the oxacillin disk method: "Surprisingly, the sensitivity of the oxacillin agar screen on MHA plates with 2% NaCl was lower than that of the 1-µg oxacillin disk diffusion method (with a high inoculum)." Felten, page 2770, 2nd column.

Felten concludes that "the cefoxitin and moxalactam **disk diffusion method** was very suitable for detection of MRSA, particularly class I isolates." *Id.*, page 2771, 1st column (emphasis added). Respectfully, Applicants submit that the teaching of Felten

would not have motivated one of ordinary skill in the art to modify the method of Merlino by substituting the cefoxitin and moxalactam used by Felten for the oxacillin and methicillin used by Merlino. The teaching of Felten would have motivated one to abandon methods using antibiotic incorporated throughout the medium, such as taught by Merlino, in favor of the disk diffusion method using cefoxitin and moxalactam. The combination of Merlino and Felten would not render Applicants' invention obvious.

The Office is using hindsight to pick and choose limitations from the prior art to find the invention obvious. Consistent with well-established Federal Circuit precedent, the Supreme Court has warned against the use of hindsight in assessing the obviousness of an invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742, 82 U.S.P.Q.2d 1385, 1397 (2007) ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."); *see also In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. . . ."). In making the instant rejection, the Office has performed exactly the same analysis faulted in *KSR Int'l* and *Dembiczak*. The mere fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. *See* Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg. 57526, 57534 (advising Office personnel applying a rational of some teaching, suggestion, or motivation in the prior art that would

have led one of ordinary skill in the art combine references that they must articulate "a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to . . . combine reference teachings . . . ."). Here, the desirability of the combination is found only in Applicants' specification. It is not found in the combined teachings of Merlino and Felten, as the Office contends.

Obviousness must be determined based on all of the evidence of record and, therefore, requires the Office to consider the entirety of a reference's teaching. *In re Evanega*, 4 U.S.P.Q.2d 1249, 1251 (Fed. Cir. 1987); *Panduit Corp. v. Dennison Mfg. Co.*, 1 U.S.P.Q.2d 1593, 1597 (Fed. Cir. 1987) (holding that in determining obviousness, a prior art patent must be considered in its entirety). The Office overlooks another teaching in Felten that undermines the conclusion of obviousness. Felten teaches that "[s]urprisingly, cefoxitin induced production of PBP2a [penicillin-binding protein 2a] in vitro in MSSA [methicillin-sensitive *S. aureus*] isolates for which cefoxitin MICs were high. . . ." Felten, page 2767, 1st column. Okonogi *et al.*, Emergence of Methicillin-Resistant Clones from Cephamycin-Resistant *Staphylococcus aureus*, J. Antimicrobial Chemotherapy, 24:637-45 (1989) ("Okonogi"),[1] cited by Felten, teaches that clinical *S. aureus* isolates resistant to cephamycin antiobiotics, such as cefoxitin, "formed penicillin-binding protein (PBP) 2′ [2a] and became phenotypically resistant to methicillin after induction with cefoxitin." Okonogi, page 637, abstract; *see also* page

[1] A copy of Okonogi has been submitted with the Information Disclosure Statement filed concurrently with this Amendment.

641. In other words, exposure to cephamycins can convert MSSA strains into MRSA strains.

Because cephamycins, such as cefoxitin, can induce resistance to methicillin in *S. aureus*, one of ordinary skill in the art at the time of the invention would not choose to use a cephamycin to screen direct or enriched patient samples for MRSA using a medium of the type disclosed in Merlino. The use of cefoxitin has the potential to create false positive results in such media, which is undesirable. Moreover, any confirmatory test of the sample from such media would also give a false positive result.

In a disk diffusion test (such as used by Felten) where one is growing a single isolate on the entire surface of a plate and looking for inhibition of growth around a disk containing antibiotic, the potential for cefoxitin to induce resistance to methicillin is not a concern because of the nature of the test. With the disk diffusion test, one can observe bacteria induced to resistance by the antibiotic in the disk. Those bacteria will grow within the zone of inhibition. In the event there is growth within the zone of inhibition, one can perform confirmatory tests on bacteria growing outside the zone, in which resistance will not have been induced, and which will not give a false positive result. Thus, in view of the nature of the disk diffusion test the potential for false positives is not a deterrent to using cefoxitin.

On the other hand, there is no zone of inhibition when using the medium of the invention because the antibiotic, for example, cefoxitin, is dispersed throughout the medium rather than diffusing outward from a disk. Bacteria capable of growing in the presence of the cefoxitin will appear at random locations on the surface of the medium. Because there is no zone of inhibition, there is no way to determine from looking at the

growth on the plate if any given colony that develops was originally resistant to methicillin, or induced to methicillin resistance by exposure to the cefoxitin in the plate, or sensitive to methicillin but resistant to cefoxitin (as were the strains discussed by Okonogi). Given that uncertainty, one of ordinary skill in the art at the time of the invention would not have been motivated to combine the teaching of Felten with that of Merlino as the Office urges, with a reasonable expectation of success.

Furthermore, in response to Applicants' arguments filed on April 30, 2007, the Office states:

> Instant claim 1 only requires that the medium comprise an antibiotic. By the disk diffusion method, antibiotic is locally applied to medium by using small disks as a carrier. However it is understood that the antibiotic diffuses through the medium in a graded fashion. Therefore, by application of the disk diffusion method as taught by Felten, for example, the medium does, in fact, contain antibiotic as required in instant claim 1.

Office Action, page 13.

As amended, claims 17-54 recite that the antibiotic is "added to the medium before the medium gels . . . ." The antibiotic, therefore, is not present in the medium in a graded fashion as occurs in the disk diffusion method taught by Felten. The conclusion that Felten teaches an antibiotic as required by claims 17-54 is incorrect.

Applicants also point out that the Office made a similar rejection based on the combination of Merlino in view of Felten during prosecution of now abandoned application no. 10/753,417. Claim 1 is representative of the rejected claims in that application:

> 1. A method of detecting antibiotic resistant microorganisms in a sample, comprising:

(a) providing a chromogenic medium, said medium comprising at least one β-lactam antibiotic, wherein said β-lactam antibiotic is not oxacillin or methicillin;

(b) incubating said sample on or in said medium; and

(c) observing that resistant microorganisms exhibit growth and non-resistant microorganisms do not exhibit growth.

Amendment dated October 18, 2005, page 3.

In that application, the Office cited Merlino as teaching that (1) 114 *S. aureus* isolates tested on CHROMagar all grew and were properly identified, and (2) methicillin resistance was confirmed by the detection of penicillin-binding protein 2a. The Office observed that Merlino does not teach cephalosporins, such as cefoxitin. Office Action mailed April 18, 2005, page 7. Felten was cited as curing that deficiency:

> Felten, F. et al teaches a method of detecting methicillin-resistant *Staphylococcus aureus* (MRSA) using cefoxitin. Felten et al teach that 100% of the MRSA were detected using the method (abstract). It would be obvious at the time the invention was made to substitute the methicillin as taught by Merlino et al with the cefoxitin of Felten et al in the method of detecting MRSA because Felten et al teach that cefoxitin is more sensitive and specific for detection of MRSA (page 2769). It would have been expected barring, evidence to the contrary, that the cefoxitin would improve the detection of MRSA since the prior art teaches that cefoxitin is a suitable alternative for oxacillin in routine antibiotic susceptibility testing.

Id.

In responding to Applicants' arguments traversing the rejection, the Office noted that Table 2 of Merlino shows 100% detection of hospital-acquired MRSA, the claims encompass detection of that subset of MRSA, and thus one of ordinary skill in the art would have had a reasonable expectation of success in combining the references. Office Action mailed January 30, 2006, page 4.

Applicants replied with two arguments. First, the failure of Merlino's method to identify 70% of community-acquired MRSA creates uncertainty undermining the allegation that the combination of Merlino and Felten would have given a person of ordinary skill in the art a reasonable expectation of success. Second, because Felten teaches that cefoxitin induced production of PBP2a *in vitro* in methicillin sensitive *S. aureus* isolates a person of ordinary skill in the art would have been concerned that using cefoxitin in the method of Merlino would cause methicillin sensitive strains to appear resistant, thus resulting in false positives. Amendment dated May 1, 2006, page 2. Those arguments were persuasive and the Office withdrew the rejection. Office Action mailed June 30, 2006, page 2.

The same arguments apply here, and they should lead to the same result. The Office has not established a *prima facie* case that Applicants' claims would have been obvious over the combination of Merlino and Felten. Accordingly, the Office should withdraw the rejection based on this combination of references.

B. Merlino in View of Felten and Boggs

The Office has maintained the rejection of claims 1 and 10-12 under Section 103(a) as allegedly being unpatentable over Merlino in view of Felten and in view of U.S. Patent No. 5,883,074 to Boggs *et al.* ("Boggs"). Office Action, page 5. The Office applies the teachings of Merlino and Felten as described above. Those references, as the Office notes, "do not expressly teach the use of cefamandole and cefotetan in a method of detecting MRSA bacteria." *Id.*

The Office finds that teaching in Boggs:

> Boggs et al teach that MRSA *S. aureus* develop resistance to numerous antibiotics (see Summary of the Invention, col 1 line 48 to col 2

> line 40, for example). Boggs et al teach that one must selectively grow MRSA *S. aureus* by including an antibiotic; this antibiotic can be cefamandole, cefoxitin or cefotetan (see col. 4 line 56 to col. 5 line 13; see col. 6, lines 13-25, for example).

Id.

In view of that asserted teaching, the Office contends that "[a] person of ordinary skill in the art at the time the invention was made would have been motivated to include cefamandole, cefoxitin, or cefotetan because Boggs et al teach that MRSA *S. aureus* are often selectively resistant to these drugs." The Office concludes that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test for MRSA resistance in *S. aureus* using S. aureus-selective chromogenic medium and cefamandole, cefoxitin, or cefotetan as selective antibiotics." *Id.*

Applicants traverse. With respect to the Office's reliance of Boggs' teaching of the antibiotics cefamandole and cefotetan, Applicants note that the pending claims do not recite either of those antibiotics. That teaching is not germane to the patentability of the pending claims.

As for the teaching of cefoxitin by Boggs, Applicants submit that combining the teaching of Boggs with that of Merlino and Felten fails to cure the deficiencies noted above in the combined teachings of Merlino and Felten. In fact, the citation of Boggs provides further evidence that the Office is using Applicants' specification as a blueprint to pick and choose elements of the claims from disparate references. Boggs discloses and claims "methods for screening compounds useful as potentiators of antibacterial agents, to compositions including such compounds, and to methods for treating bacterial infections using such compositions." Boggs, column 3, lines 48-51. The potentiators "exhibit little or no antibacterial activity when used alone and which are not

primarily anti-β-lactamases, but which can induce susceptibility to an antibacterial agent in a bacterium resistant to that agent when the potentiator is used in conjunction with the antibacterial agent." *Id.*, lines 51-58. Respectfully, that teaching bears no relevance to the Applicants' invention, and thus provides no evidence supporting the Office's conclusion that combining the teaching of Boggs with that of Merlino and Felten renders Applicants' invention obviousness.

Nonetheless, citing column 4, line 65, to column 5, line 13 and column 6, lines 13-25, the Office asserts that "Boggs et al teach that one must selectively grow MRSA *S. aureus* by including an antibiotic; this antibiotic can be cefamandole, cefoxitin or cefotetan." Office Action, page 5. Neither passage, however, mentions methicillin resistant *S. aureus*. The first describes steps of a method for identifying potentiators for an antibacterial agent to which a bacterium is resistant. The second passage provides a list of "potentiated antibacterial agent[s]" of which cefoxitin is one of many possibilities. Nothing in the passage links cefoxitin, nor any of the other antibiotics listed, to *S. aureus* or to MRSA. The Office is picking and choosing from the reference using hindsight. That is not permitted. *Dembiczak,* 50 U.S.P.Q.2d at 1617.

For the reasons of record, and for those set forth here, Applicants submit that Merlino in view of Felten and Boggs do not render their invention obvious.

C. Merlino in View of Felten and Dorso

Claims 1 and 10-12 also stand rejected under Section 103(a) as allegedly obvious over Merlino in view of Felten, and in view of U.S. Patent No. 6,221,859 to Dorso *et al.* ("Dorso"). Merlino and Felten are applied as above. The Office

acknowledges that the combination of those references does not teach the use of cefmetazole in a method for detecting MRSA bacteria. Dorso is cited as teaching a method for treating antibiotic resistant pathogenic bacteria, including *S. aureus*. According to the Office Dorso "teach[es] that cefmetazole is among the antibiotics that are losing efficacy against pathogenic bacteria, and must be combined with other compounds to enhance treatment." *Id.* (citation omitted). From this teaching the Office concludes that "[a] person of ordinary skill in the art at the time the invention was made would have been motivated to include cefmetazole in a selective medium for detecting resistant *S. aureus*, because Dorso et al teach that cefmetazole is a compound that is subject to bacterial resistance, and Felten et al and Merlino teach a method of detecting *S. aureus* with resistance to a given antibiotic." *Id.*

Applicants traverse the rejection. Combining the teaching of Dorso with that of Merlino and Felten does not cure the deficiencies of those two references. Dorso teaches "novel 2-(naphthosultamyl) methyl-carbapenem antibacterial agents or pharmaceutically acceptable salts thereof in combination with other β lactams, which are useful in treating and preventing . . . methicillin resistant *Staphylococcus aureus*." Dorso, abstract. The Office cites to column 8, line 63, to column 9, line 10, as teaching "that cefmetazole is among the antibiotics that are losing efficacy against pathogenic bacteria, and must be combined with other compounds to enhance treatment." Office action, page 6. Even if that characterization were correct, which it is not, it has nothing to do with Applicants' invention. Applicants' invention is not directed to a combination of antibiotics for treatment of bacterial infections. The section of Dorso upon which the Office relies is nothing more than a list of β lactam antibiotics that may be combined

with the novel 2-(naphthosultamyl) methyl-carbapenem antibacterial agents which are the basis of the Dorso invention. Respectfully, nothing in the cited section supports the Office's interpretation of Dorso as teaching that cefmetazole is losing efficacy against pathogenic bacteria.

Again, the Office is using hindsight to pick and choose one element of the claimed invention (cefmetazole) from a reference, which when considered in its entirety, is clearly not directed to media, chromogenic or otherwise, for detection of any bacteria, much less MRSA. The use of hindsight is impermissible. The combination of Merlino in view of Felten and Dorso does not render Applicants' invention obvious.

D. Merlino in View of Felten and Hanaki

The Office has also maintained the rejection of claims 1 and 10-12 under Section 103(a) as allegedly unpatentable over Merlino in view of Felten, and further in view of U.S. Patent No. 6,294,527 to Hanaki ("Hanaki"). Office Action, page 7. The Office applies the teachings of Merlino and Felten as discussed above, noting that the combination of references "do not expressly teach the use of flomoxef in a method of detecting MRSA bacteria." *Id.* Hanaki is cited as teaching the "use of flomoxef-doped plates as a control for testing other compounds against *S. aureus*." *Id.* According to the Office, the "[u]se of flomoxef as a control distinctly shows its use for characterizing MRSA *S. aureus* versus non-resistant *S. aureus*." *Id.* In view of that alleged teaching, the Office concludes that "[a] person of ordinary skill in the art at the time the invention was made would have been motivated to include flomoxef in a selective medium for detecting resistant *S. aureus*, because Hanaki et al. teach that flomoxef is a compound that is subject to bacterial resistance, and Felten et al and Merlino et al teach a method of detecting *S. aureus* with resistance to a given antibiotic." *Id.*

Applicants traverse. The teaching of Hanaki does not cure the deficiencies argued above in the combination of Merlino and Felten. Hanaki is cited as teaching the use of flomoxef as a control in evaluating new antibiotics, which does not address the issues raised by Applicants concerning Merlino and Felten. In view of the deficiencies in the combined teachings of those references, the Office has not established the *prima facie* obviousness of Applicants' invention.

E. Merlino in View of Felten and Rambach

The Office has maintained the rejection of claims 1, 3, 7, 8, and 10-12 as allegedly unpatentable under Section 103(a) over Merlino in view of Felten, and further in view of U.S. Patent No. 6,548,268 to Alain Rambach ("Rambach"). Office Action, page 8. Applicants traverse the rejection.

The Office applies Merlino and Felten as described above, noting, however, that the combination of those references does not expressly teach the use of 5-bromo-4-chloro-3-indoxyl glucoside, 5-bromo-6-chloro-3-indoxyl-phosphate, or 5-bromo-4-chloro-3-indoxyl glucuronide as chromogenic agents. *Id.* The Office looks to Rambach to supply the missing teaching. According to the Office:

> A person of ordinary skill in the art at the time the invention was made would have been motivated to use the chromogenic substrates taught by Rambach et al in a method of detecting MRSA *S. aureus* taught by Merlino et al and Felten et al, because Merlino et al teach that chromogenic substrates can be used to detect MRSA *S. aureus*, Felten et al teach that cefoxitin and moxalactam can be used to detect low-resistance MRSA *S. aureus*, and because Rambach teaches that *S. aureus* can be specifically identified by growing on the chromogenic substrates identified in his patent publication.

Id., page 5.

Applicants have discussed the deficiencies in the combination of Merlino and Felten. Those arguments also apply to this rejection. Adding the teaching of Rambach does not cure those deficiencies. Rambach is merely cited as teaching particular compounds as chromogenic agents for use in media for detecting *S. aureus,* which does not address the issues raised above by Applicants. In view of those deficiencies in the combined teachings of Merlino and Felten, the Office has not established the *prima facie* obviousness of Applicants' invention.

F. Merlino in View of Felten, Carricajo, and Pead

The Office newly rejects claims 1, 10, 11, and 14 under 35 U.S.C. § 103(a) as allegedly unpatentable over Merlino in view of Felten, in view of A. Carricajo *et al.*, Comparative Evaluation of Five Chromogenic Media for Detection, Enumeration, and Identification of Urinary Tract Pathogens, Eur. J. Microbiol. Infect. Dis., 18:796-803 (1999) ("Carricajo"), and in view of L. Pead *et al.*, Staphylococci as Urinary Pathogens," J. Clin. Pathol., 30:427-31 (1977). Office Action, page 9. Applicants traverse this rejection.

The Office applies Merlino and Felten as described above. According to the Office, "[n]either reference expressly teaches that samples should be directly taken from patients without further manipulations of the samples." *Id.*, page 10. The Office cites Carricajo as "teach[ing] that one can test clinical urine specimens by direct inoculation onto chromogenic media," and as "teach[ing] that types of staphylococci can be differentiated by inoculating small samples of urine directly onto CHROMager with an inoculating loop." *Id.* (citation omitted).

The Office cites Pead as "teach[ing] that in a survey of staphylococcus as determined from urine samples, *S. aureus* is responsible for 16% of infections (see Abstract, p. 427)." *Id.*

According to the Office:

> A person of ordinary skill in the art at the time the invention was made would have been motivated to test clinical samples for the presence of *S. aureus* by direct inoculation of clinical samples onto a chromogenic medium because Carricajo et al teach that one can directly inoculate urine onto CHROMager medium and observe development of staphylococcus specimens, and Pead et al teach that *S. aureus* infections are a

substantial fraction of staphylococcus infections as determined by urine samples.

Id.

Combining the teaching of Carricajo and Pead with that of Merlino and Felten does not cure the deficiencies of the latter two references. Neither Carricajo nor Pead provide a teaching that would motivate one of ordinary skill in the art to modify the medium of Merlino as the Office concludes would have been obvious in view of the teaching of Felten. None of the chromogenic medium disclosed in Carricajo contain antibiotics, nor does the reference address detection of MRSA. Pead is even less relevant. It merely teaches that Staphylococci may be isolated from urine. Those teachings, when combined with the teachings of Merlino and Felten, would not render Applicants' invention obvious.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: January 10, 2008

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APPENDIX 1

Current Claims	Prior Claims	Support in the Specification
17	1	[0009]-[0012], [0022]
37	1	[0009]-[0012], [0022]
52	14	[0043]-[0046]
78	14	[0043]-[0046]
18, 38, 56, 82	3, 7	[0034]
19, 39, 57, 83	12	[0037]
20, 40, 58, 84		[0037]
21, 41, 59, 85	16	[0034]
22, 42, 60, 86		[0037]
23, 42, 61, 87	8	[0038]
24, 44, 62, 88		[0037]
25, 45, 63, 89		[0037]
26, 46, 64, 90		[0009]
27, 47, 65, 91	10	[0041]
28, 66	1	[0025]
29, 66	1	[0026]
30, 68	1	[0027]
31, 48, 69, 92	11	[0029]
32, 49, 70, 93		[0040]
33, 50, 71, 94		[0040]
34, 72		[0025], [0034]
35, 73		[0026], [0034]
36, 53, 74, 95		[0039]
53, 79		[0013]
54, 80		[0013]
55, 81		[0013]
75, 96		[0047]
76, 97		[0047]
77, 98		[0067]